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Original Article

Are there differences in hepatitis-B immunization status between diabetes and non-diabetes subjects in Korea?

Ji Young Park[1], Su Kyoung Kwon[2]

[1]*Department of Internal Medicine, Division of Infection, College of Medicine, Kosin University, Busan, Korea*
[2]*Department of Internal Medicine, Division of Endocrinology and Metabolism, College of Medicine, Kosin University, Busan, Korea*

Objectives: The American Diabetes Association (ADA) recommends hepatitis-B virusVIruS vaccination for unvaccinated adults with diabetes. However, the Korean Diabetes Association (KDA) did not recommend hepatitis-B vaccination for unvaccinated adults with diabetes. This study was performed to assess the differences in hepatitis-B virus antigen and antibody status between Korean patients with diabetes and those without by using national survey data.
Methods: We analyzed hepatitis-B virus antigen and antibody status in 9,771 South Korean people from the general population based on the Korean National Health and Nutrition Examination Survey. Diabetes patients were defined as those with a measured fasting plasma glucose over 126 mg/dL or those who had been previously diagnosed with diabetes by other health care centers.
Results: Subjects with diabetes accounted for 812 (8.3%) among the 9771 study subjects. The prevalence ofhepatitis-B (HBsAg) seropositive subjects was not significantly different (3.9% vs. 4.6%, P = 0.09) between subjects with diabetes and those without. The prevalence of hepatitis-B antibody (HBsAb) positive subjects and unimmunized subjects was not significantly different (55.2% vs. 58.2%, P = 0.09, 40.9% vs. 37.2%, P = 0.09) between the two groups. The prevalence of unimmunized subjects decreased by age (< 20 years 33.3 % vs. 33.0%, 20~29 years 49.1% vs. 41.2%, 30~39 years 41.9% vs. 37.7%, 40~49 years 35.1% vs. 33.5%, 50~59 years 39.0% vs. 38.0%, 60~69 years 41.2% vs. 39.8%, > 70 years 48.5% vs. 42.8%) but was not significantly different between the 2 groups.
Conclusions: From this study, we conclude that there are not sufficient grounds to recommend routine hepatitis-B virus vaccination for unvaccinated Korean subjects with diabetes at this point in time in Korea. Further prospective studies will be needed.

Key Words: Diabetes, Hepatitis B, Immunization, Korean National Health and Nutrition

Diabetes is a disorder characterized by high blood glucose due to decreased pancreatic insulin secretion with or without increased peripheral insulin resistance, and it is a systemic metabolic disorder which can lead to the development of other diseases caused by hyperglycemia associated chronic complications, and an increased mortality rate. Generally, it is known that atherosclerotic cardiovascular disease is a major cause of morbidity and mortality of diabetes; however, the dysfunction of immune cells in high blood glucose level can increase the morbidity and mortality rate

Corresponding Author: Su Kyoung Kwon, Department of Internal Medicine, College of Medicine, Kosin University, 262, Gamchen-ro, Seo-gu, Busan 49267, Korea
Tel: +82-51-990-6712 Fax: +82-51-990-6712 E-mail: mir316@naver.com

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of infectious diseases. For this reason, a vaccination to prevent several infectious diseases is recommended.[1,2]

Based on the data of the US Centers for Disease Control and Prevention (CDC), the American Diabetes Association (ADA) has recommended the hepatitis B virus vaccination for adult patients with diabetes aged 19 or more since 2013. As of 2015, the Korean Diabetes Association (KDA) recommends that adult diabetic patients receive the vaccination for pneumococcus and influenza, not the hepatitis B virus.[2,3] The reason why CDC recommended hepatitis B vaccination for diabetic patients in the US is based on the following: A repeat outbreak of hepatitis B occurred among patients with diabetes; a large-scale epidemiological survey demonstrated a significant increase in core antibodies among diabetic patents which is an indicator of hepatitis B virus infection.[4,5]

In Korea, there has been no study on whether or not there is any difference in the prevalence of acute and chronic hepatitis B between diabetic patients and non-diabetic subjects. And there is no vaccination recommendation or guidelines related to this matter in Korea.

Using Korean National Health and Nutrition Examination Survey (KNHANES) data, this study intends to analyze whether or not there is any difference in the prevalence of hepatitis B between Korean adult diabetic patients and non-diabetic research subjects, and to review whether or not differentiated vaccination recommendation for hepatitis B virus is necessary for Korean patients with diabetes.

MATERIALS AND METHODS

Research subjects

This study carried out an analysis using the data obtained in the KNHANES conducted by the Korea Centers for Disease Control and Prevention (KCDC) under the Ministry of Health and Welfare. The KNHANES was conducted every three years from 1998 to 2005 and has been conducted every year since 2007. At first, the subjects from the KNHANES conducted from 1998 to 2012, aged 10 or more who went through a health interview survey and a health examination survey were selected. Next, an analysis was conducted targeting research subjects of the health examination survey who received both HBsAg and HBsAb tests. The data included in this study resulted from that analysis.

The KNHANES was conducted with the approval of the Research Ethics Committee under Korea Centers for Disease Control and Prevention (Approval No.: 2007-02-CON-04-P, 2008-04EXP-01-C, 2009-01 CON-03-2C, 2010-02CON-21-C, 2011-02CON-06-C). Under 'Personal Information Protection Actj, with the exception of data available to identify research subjects (the date of survey, the name of detailed administrative district), the remaining survey data was obtained from the data office of Korea Centers for Disease Control and Prevention and used for analysis.

Data collection

The KNHANES is classified into a health survey and a nutrition survey. The health survey is classified into three categories: health interview survey, health knowledge and behavior survey, and health examination survey.

The data selected and used for analysis included the following: health interview survey items such as age, gender, and whether a person was diabetes or non-diabetes; health examination survey items such as HBsAg and HBsAb; body measurement items such as blood pressure, body weight, height and abdominal circumference; blood test items such as fasting plasma glucose and liver enzyme level.

Body measurement was carried out on research subjects who were fasting (abstaining from food) and clad in light clothes by a proficient nurse using a standardized method. The blood test was carried out with blood drawn from the median vein when the subj ects had fasted for at least 10 hours and with all blood samples stored in a refrigerator. The serum test was carried out with serum centrifuged within 30 minutes and sealed and stored in a refrigerator. Both the blood test and serum test were carried out by the Central Clinical Laboratory.

HBsAg and HBsAb was analyzed using ELISA test (CODA of BIO-RAD, USA); total cholesterol, triglyceride, blood glucose, AST (aspartate aminotransferase, SGOT), ALT (alanine aminotransferase, SGPT) and creatinine using Hitachi-747 autoanalyzer; CBC (Complete Blood Count) using Cell-Dyn 1300 Auto cell counter.

HBsAg positive and HBsAb negative subjects were classified as hepatitis-B earnerscarriers;

HBsAg negative and HBsAb negative subjects as non-immunized persons; HBsAg negative and HBsAb positive subjects as persons immunized to hepatitis B. Diabetes subjects are defined as people having a fasting blood glucose level of 126 mg/dL or greater in the health examination survey and answering that they were diagnosed with diabetes in the health interview survey.

Statistical analysis

All data was analyzed without weighting using original data by survey year. An analysis was carried out using SPSS (version 18.0, USA), T-test, ANOVA, ANCOVA and chi-square test. Each mean value was expressed using mean value ± standard deviation or mean value ± standard error. It was decided that there was a statistical significance if a P value was less than 0.05.

RESULTS

General characteristics of research subjects

Among a total of 161,488 persons who received the KNHANES, 9,771 were finally selected. Of these, 812 of the total research subjects (8.3%) were patients with diabetes. Compared to non-diabetic subjects, diabetic subjects were older (mean value of 51.66 vs 37.91), had significantly higher body weight, body mass index (BMI) and

Table 1. Baseline characteristics of study subjects

Variables	Diabetes (n = 812)	Non diabetes (n = 8959)	*P*-value
Male : Female	415:397	4095:4864	0.021
Age, years	51.66 ± 15.67	37.91 ± 18.07	< 0.001
Weight, Kg	62.07 ± 10.81	58.8 ± 11.34	< 0.001
BMI, kg/m2	24.02 ± 3.41	22.47 ± 3.38	< 0.001
Waistcircumference(WC)	84.87 ± 9.34	77.75 ± 10.14	< 0.001
SBP, mmHg	134 ± 20.76	122.74 ± 18.75	< 0.001
DBP, mmHg	80.75 ± 12.44	75.99 ± 12.53	< 0.001
Pulserate, bpm	76.13 ± 10.88	74.02 ± 10.40	< 0.001
AST, U/L	51.66 ± 15.67	26.91 ± 18.52	< 0.001
ALT, U/L	33.84 ± 29.725	25.59 ± 21.30	< 0.001
Fastingbloodglucose, mg/dL	163.25 ± 62.04	93.65 ± 12.82	< 0.001
WBC, × 103/μL	6.15 ± 1.83	6.20 ± 18.28	0.947

Data are presented by mean ± standard deviation.
N, number; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beats per minuite; AST, aspartate aminotransferase; ALT, alanine aminotransferase; WBC, white blood cell.

waist circumference (WC) because of obesity, and also had significantly more cardiovascular risk factors such as blood pressure and pulse rate and AST and AL T values (Table 1).

It is said that obesity rates increase with age and that the increased prevalence of obesity among diabetic patients can increase the prevalence of nonalcoholic fatty liver disease. For this reason, AST and ALT values were analyzed after adjustment for age and BMI, and age, BMI and WC respectively. After the adjustment for age and anthropometric differences, the AST and ALT values between subjects with diabetes and those without showed a statistically significant difference (Table 2).

Hepatitis-B immunization status for diabetic subjects and non-diabetic subjects

Table 2. Age and Obesity adjusted means of liver function

Variables	Diabetes (n = 812)	Non diabetes (n = 8959)	*P*-value
Aspartate aminotransferase, AST, SGOT*	30.71 ± 0.69	27.07 ± 0.21	< 0.001
Alanine aminotransferase, ALT, SGPT*	31.35 ± 0.75	25.83 ± 0.23	< 0.001
AST**	30.12 ± 0.69	27.13 ± 0.21	< 0.001
ALT**	30.17 ± 0.75	25.95 ± 0.23	< 0.001

Data are presented by mean ± standard error
*Adujusted by age and body mass index.
** Adjusted by age, body mass index and waist circumference.

Among a total of 812 subjects with diabetes, 32 subjects were hepatitis B patients or hepatitis B carriers considered to be HBsAg positive and HBsAb negative, accounting for 3.9% of the total patients. Patients without HBsAg and HBsAb were classified as persons who were non-immune to HBV and susceptible to HBV, and their number was 332, 40.9% of the total patients. Persons who acquired immunity to hepatitis B with HBsAb and without HBsAg were classified as persons immune to HBV, and their number was 448 of the total patients (55.2%). Among a total of 8,959 research non-diabetic subjects, the number of HBV carriers was 412, 4.6% of the total subjects; the number of persons non-immune to HBV was 3,329, 37.2% of them; the number of immunized persons antibodies to HBV was 5,218 of them (58.2%). From the results of chi-square analysis on the state of having antigen and antibody, it was shown that there was not a significant difference in hepatitis-B immunization status between diabetic subjects and non-diabetic subjects (Fig. 1. P = 0.096).

Hepatitis-B immunization status depending on age group and diabetes statue

The prevalence of diabetes increased with age: 1.5% (27 persons) for lOs; 3.7% for 20s; 6.3%, for 30s; 8.2% for 40s; 16.7% for 50s; 16.4% for 60s; 16.1% for 70s. Among diabetic patients in their lOs, HBV carriers accounted for 3.7%; persons immune to HBV 63%; persons non-immune to HBV 33.3%. Among non-diabetic patients in their teens, HBV carriers accounted for 2.4%; subjects immune to HBV 64.6%; subjects non-immune to HBV 33%. There was not a significant difference

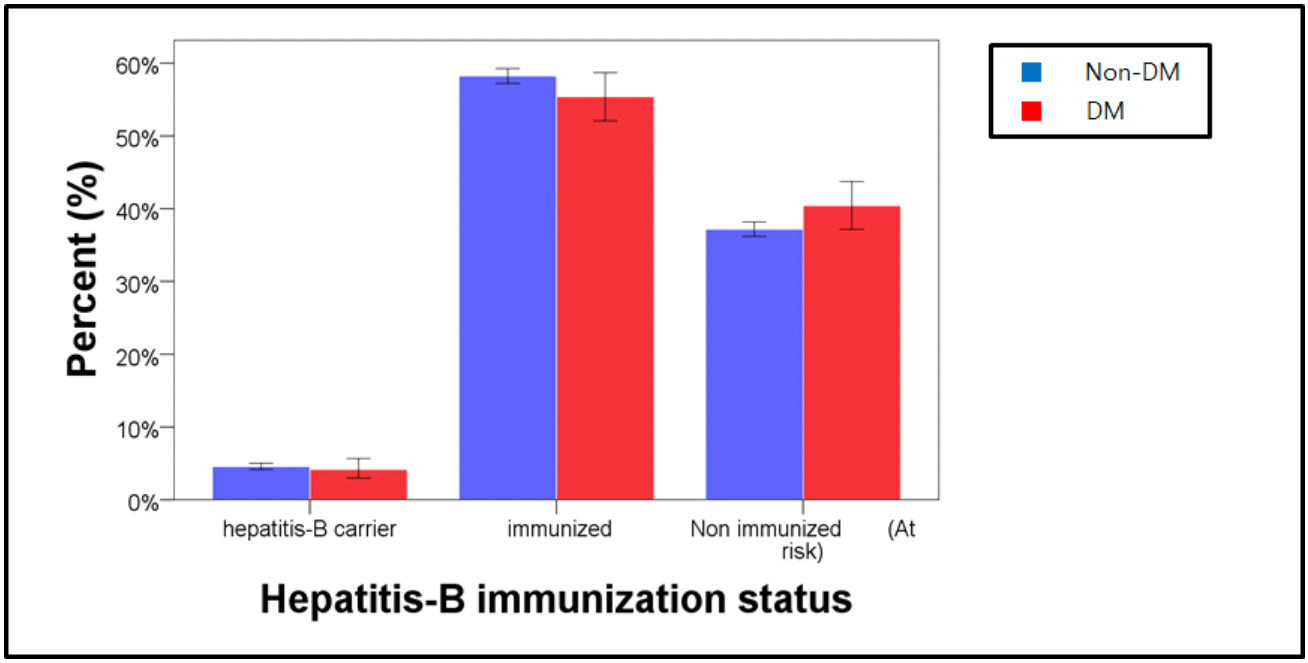

Fig. 1. Distribution of hepatitis-B immunization status among diabetes and non-diabetes subjects.

in hepatitis-B immunization status between all diabetic and non-diabetic subjects. This result did not show a significant difference in all age groups, from twenties to se venties or older (Table 3).

DISCUSSION

As the KNHANES was carried out targeting the whole nation divided according to districts and ages, the survey data can claim to be representative and reliable, and reflects relatively well the overall situation in Korea.

According to the result of this study, there is no evidence that there is a difference in the carriage of and immunity to HBV between diabetic subjects and persons without diabetes. This appears almost the same in not only for those in their lOs and 20s - considered as generations born after the introduction of nationwide hepatitis B vaccination - but also the elderly who are less likely to be vaccinated. So, it is proper for the Guidelines not to recommend uniform vaccination for diabetic patients.[3] Korea introduced the hepatitis B vaccination in 1983 and started collective vaccination for school-age children around 1988. Regular vaccination has been carried out for babies and children since 1995. Consequently, the prevalence of hepatitis B has sharply decreased among the younger generation, and an additional vaccination against hepatitis B caused by diabetes would seem to have little value.[6]

The ADA has continuously recommended hepatitis B vaccination for patients with diabetes since it first released a guideline for recommending hepatitis B vaccination for diabetic patients in 2013.[2] The recommendation for hepatitis B vaccination of ADA was based on the reports of CDC at the time of the revision in 2013. In the

Table 3. Distribution of hepatitis-B immunization status according to different age groups by diabetes status

Age Groups	Non-diabetes			Diabetes			*P*-value
	HBV carrier	Immunized	Non-immunized	HBV carrier	Immunized	Non-immunized	
Total(%)	408 (4.6%)	5189(58.2%)	3313 (37.2%)	36 (3.9%)	477 (55.2%)	348 (40.9%)	0.169
〈20	42 (2.4%)	1152 (64.6%)	588 (33.0%)	1 (3.7%)	17 (63%)	9 (33.3%)	0.898
20-30	81 (5.6%)	764 (53.1%)	593 (41.2%)	0 (0.0%)	28 (50.9%)	27 (49.1%)	0.140
30-40	115 (6.2%)	1033 (56.0%)	696 (37.7%)	8 (6.5%)	64 (51.6%)	52 (41.9%)	0.622
40-50	77 (5.1%)	918 (61.4%)	501 (33.5%)	5 (3.7%)	82 (61.2%)	47 (35.1%)	0.747
50-60	63 (6.0%)	588 (56.0%)	396 (38.0%)	6 (2.9%)	122 (58.1%)	82 (39.0%)	0.188
60-70	21 (2.5%)	486 (57.7%)	335 (39.8%)	10 (6.1%)	87 (52.7%)	68 (41.2%)	0.078
70-80	10 (2.5%)	218 (54.1%)	175 (43.4%)	1 (1.1%)	45 (51.1%)	42 (47.7%)	0.605
≥ 80	3 (3.2%)	54 (57.4%)	37 (39.4%)	1 (5.3%)	8 (42.1%)	10 (52.6%)	0.463

HBV, hepatitis B virus; Immunozed, HBsAg (-) and HBsAb (+); Non-immunized, HBsAg (-) and HBsAb (-)

US, 29 incidents of the outbreak of hepatitis B since 1996 has been reported and this occurred in long-term care facilities. Among these 29 incidents, 25 occasions occurred among diabetic patients who had received assisted blood glucose monitoring.[5,7,8] So, after evaluating the risk of hepatitis B for diabetic patients through scientific data investigation, the Advisory Committee on Immunization Practices (ACIP) recommended vaccination for all diabetic patients aged 19 to 59 who had not been vaccinated but diabetic patients aged 60 or more were excluded from the recommendation because they had little chance of contracting hepatitis B.[2] In the case of diabetic patients having little chance of contracting the hepatitis B infection, Reilly et al. reported that the accompaniment of diabetes increases 2.1 times CCI = 1.6-2.8) the risk of acute hepatitis B infection for patients aged 23 to 59 and 1.5 times CCI = 0.9-2.5) for patients aged 60 or more.[9] According to the results from the US National Health and Nutrition Examination Survey conducted from 1999 to 2010, the positive rate of HBcAb indicative of HBV infection in the past or in the present was 60% ($P < 0.001$) higher in diabetic patients aged 18 or more, and the prevalence increased 1.7 times CCI = 1.3-2.2) in patients aged 10 to 59 when age was adjusted.[5]

This study identified the state of hepatitis B through only HBsAg and HBsAb status and HBcAb was not included in the KNHANES data. So, it cannot be determined whether the presence of acute hepatitis B or the acquisition of HBsAb by persons could be attributed to natural immunity or vaccination. The levels of AST and ALT which indicate acute liver inflammation were significantly increased even after the adjustment for age and obesity. This seems to suggest the likelihood of a coexistence of acute inflammatory condition such as acute hepatitis B. However, no adjustment was made to take into account differences in alcohol intake or presence of hepatitis C, which are known to be increased in diabetic patients.[10-12]

So, it is not proper to interpret the elevation of AST and ALT as the result of an outbreak of acute hepatitis B in this study.

It is uncertain whether or not there is a direct causal relationship between diabetes and hepatitis B. However, it has been reported that in a case where a diabetes patient develops acute hepatitis B, the clinical results can be fatal compared to a non-diabetic patient and the morbidity rate of chronic hepatitis is high among diabetes patients.[9,13] As mentioned above, diabetes tends to be accompanied by nonalcoholic steatohepatitis or hepatitis C. The outbreak of these diseases increases the risk of the development ofliver cirrhosis or liver cancer. Thus, it is necessary to pay attention to any outbreak of liver disease and to try to prevent it.[14]

HBV is a virus invulnerable to the external environment, having high infectivity. Its infection can spread through medical instruments contaminated by blood having infectivity.[15] Actually, a collective outbreak of acute hepatitis B in the US occurred that was centered on diabetic pa-

tients in a long-term care sanatorium. The major cause is believed to be the sharing blood glucose testing equipment and blood collection supplies that were not properly disinfected.[4,7,16] Even if diabetic patients receive vaccinations on three occasions, they more frequently fail to produce the appropriate level of antibody with age. So, additional vaccinations are recommended, but concrete guidelines for this have yet to be established.[17]

This study reviewed whether there is any difference in hepatitis B immunization status between diabetic subjects and non-diabetic persons in Korea, and conducted an analysis using representative and reliable data to identify whether there is any reason for the recommendation of vaccination for diabetic patients who have not received it. However, only limited data can be acquired about hepatitis B because of the limitation of the survey in which a wide range of public health issues were set. So, it cannot be known whether or not acute hepatitis B occurred and whether it was the vaccination or the immune response after infection that enabled people to acquire the necessary antibodies. Furthermore, there is a limitation with regard to the analysis, because it could not be known whether or not hepatitis C existed. As the data was limited to the results of the survey, the number of subjects with diabetes, especially aged less than 20 and 70 or more was small, and so the analysis was not broad. In addition, it could not be determined whether or not testing devices and medical instruments shared by many people were used. So this was another weakness with the analysis.

In conclusion, as there is no statistical difference in hepatitis B immunization status between subjects with diabetes and those without in Korea, it cannot be said that diabetes itself increases hepatitis B. As nationwide postnatal hepatitis B vaccines are currently administered to almost all babies and children in Korea, the number of adults that require vaccination is expected to decrease further in the future. So, it is not proper to recommend uniform vaccination to all adult diabetic patients who have not been vaccinated.

However, in the situation where a patient must undergo frequent blood tests because of the outbreak of disease and there is a great possibility of being exposed to medical instruments contaminated by another person's blood while the patient is admitted to a long-term care facilities, it is desirable to consider administering the hepatitis B vaccination.[4,16]

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